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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	8

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/320,767	GIANNOUKAKIS ET AL.	
	Examiner	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *10 July 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 20-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,20-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's amendments filed on 7/10/00 in Paper No. 6 has been entered. Claims 13-19 have been canceled, and newly added claims 20-30 have been entered. Claims 1-12 and 20-30 are currently pending in the present application.

Claim Rejections - 35 U.S.C. § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 5, 9, 20-25 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a product or method for reducing beta-cell dysfunction in an individual with a pancreatic disorder comprising administering a nucleic acid encoding any IL-1 beta inhibitor, or any inhibitor of fas mediated apoptosis . These are drawn to a broad genus of inhibitors which have not been described in the specification. The specification does not describe each and every IL-1 beta inhibitor or inhibitor of fas mediated apoptosis to convey to one skilled in the art that the applicant had possession of the claimed invention. The specification does not describe any nucleotide sequence

encoding such inhibitor proteins except state that such nucleic acid molecules are known in the art and can be isolated from a variety of different sources including but not limited to vertebrates, mammalian and human sources, without undue experimentation. (See page 18 of specification.) The specification however, refers to specific IL-beta inhibitors such as IL-1Ra, IGF-1 and IRAP whose nucleotide sequences are known.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With no guidance as to the structures of the nucleotide sequences encoding the IL-1 beta inhibitors claimed, the skilled artisan cannot envision the detailed chemical structures of the encompassed polynucleotides, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, of the IL-1 beta inhibitors claimed, only IL-1Ra, IGF-1 and IRAP, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

4. Claims 20-30 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for constructing adenoviral vectors with or without E1 and E3 deletions comprising the (i) IL-1Ra gene with a CMV promoter and (ii) IGF-1 gene with a SV40 promoter and (iii) lentiviral vector comprising the IL-1Ra gene, does not reasonably provide enablement for any recombinant viral vector comprising any sequence encoding an inhibitor of IL-1 beta activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to any recombinant viral vectors, retroviral vectors, adeno-associated viral vectors, herpes simplex viral vectors, lentiviral vectors comprising any inhibitor of IL-1 beta activity or wherein inhibitor is a NF-kappa beta.

No other vectors are described with any particularity, except adenoviral vectors. Particular guidance regarding construction of the vector is required. Vector construction requires undue experimentation with regards to selection of promoters and enhancers

for the specific IL-1 beta inhibitor gene sequence inserted, (in addition to the deletion of specific viral genes which may have adverse effects on delivery), that encodes a protein having the effect of IL-beta inhibition. The specification did not teach any and all IL-beta inhibitors and it would require undue experimentation to make a vector with any IL-beta inhibitor because it is not clear which encoded proteins would have that effect.

5. Claims 1-12 stand rejected under 35 U.S.C 112 first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims directed to (1) a method for the reduction of beta cell dysfunction and hence treatment of an individual with pancreatic disease and (2) a method for reducing Fas mediated beta cell apoptosis in an individual with a pancreatic disease and hence treatment of the same, by the administration of recombinant viral vectors are not enabled. In addition to the reasons presented above, the specification does not enable any person skilled in the art to which it pertains, or to which it is most nearly connected, to use the invention, and is repeated for the same reasons of record as set forth in the Official action mailed 1/4/00 in Paper No. 4.

Applicants arguments filed 7/10/00 have been fully considered but were not found persuasive.

Applicants argue that there have been indeed recently confirmed successes in human gene therapy trials, and directs Examiner's attention to Exhibits A and B. While

Cavazzana-Calvo reports on the successful use of gene therapy for the treatment of inherited severe combined immunodeficiency (SCID), published in Science, April 2000, and while a review article by Anderson references recent publications that suggest progress in gene therapy for the treatment of hemophilia, the examiner maintains that at the time of applicant's filing May 1999, the art remained very immature and highly unpredictable as there was no confirmed success in any human gene therapy trial, involving a method of reducing beta cell dysfunction in an individual with a pancreatic disorder. The limited successes in the art cannot broadly be interpreted as predictable or extrapolatable to non-analagous methods.

Applicant's assert that the specification as filed discloses specific regulators; methods for deriving nucleic acid molecules; recombinant expression vectors; methods for transfer and expression of nucleic acid molecules; methods for determining effective doses; in vivo methods of administering nucleic acids; ex vivo methods of administering pancreatic cells to host; and co-administration of specific immunosuppressive agents to prevent graft rejection; and maintains that one skilled in the art could without undue experimentation, practice the claimed methods or invention by following the teachings of the specification. However, this argument was not found persuasive and is repeated for the same reasons of record as cited in the previous Official action mailed 1/4/00 in Paper No. 4. While the specification discloses general teachings regarding regulators and expression vectors, and methods for determining effective doses to name a few, it would require undue experimentation to determine a specific gene delivery system which delivers high levels of expression in cells; the number of transfectants

therapeutically effective in reducing beta cell dysfunction and the route of administration, in a method of treating an individual with a pancreatic disorder by reducing beta-cell dysfunction in said individual. Further, the teachings in the specification are directed to in vitro methods of efficiently infecting human islets cells with adenoviral vectors and it remains unclear how the in vitro success is generally correlative of in vivo human successes in the reduction of beta-cell dysfunction in an individual with a pancreatic disorder.

Applicants further argue that a patent need not teach and preferably omits what is well known in the art, and asserts that given the teachings of the specification and general knowledge that is well known in the art, that one skilled in the art could readily prepare and utilize the claimed vectors without undue experimentation. While vector preparation and utilization *in vitro*, may be well known in the art and may be prepared without undue experimentation as claimed by applicant, the examiner contends that the specification as filed presents undue experimentation for one skilled in the art as one must by trial and error experimentation, determine which recombinant lentivirus vector, or which recombinant adeno-associated viral vector, or which recombinant herpes simplex viral vector, or which recombinant E1 and E3 deleted adenoviral vector, or which recombinant adenoviral vector comprising modified E2 and E4 regions, comprising a nucleic acid molecule encoding some inhibitor of IL-1 beta activity, when introduced into a beta cell and transplanted into an individual, would be therapeutically effective in reducing beta-cell dysfunction in an individual with a pancreatic disorder. Therefore, the claims stand rejected for reasons of record.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (U.S. Pat. NO: 5,977,341), in view of Monia et al. (U.S. Pat. NO: 5,962,673), and further in view of Crawford et al.(U.S. 6,107, 057), and Robbins et al.

Claims 20 and 25 are directed to a recombinant retroviral vector comprising a nucleic acid molecule encoding any inhibitor of IL-1 beta activity and specifically an inhibitor of NF-kappa B activity, respectively.

Monia et al. (Pat. No. 5,977,341) teaches that NF-kappa-B normally exists in the cytoplasm bound to a family of inhibitor proteins known as IKB-alpha and IKB-beta. (See col. 1, lines 43-49).

Monia et al. in Pat No. 5,977, 341 did not teach the nucleotide sequence encoding IKB alpha.

Monia et al. (Pat. No. 5,962,673) taught nucleic acids encoding Inhibitor-kappa B kinase alpha.

Monia does not expressly disclose that the IKB-alpha gene is inserted into a retroviral vector.

However, recombinant DNA technology has revolutionized the way genes can be inserted into different vectors and expressed by means of specified promoters.

One of ordinary skill in the art would have been motivated to do this as Crawford stated that methods for introducing heterologous polynucleotides into mammalian cells are known in the art and include viral infection. (See col. 6, lines 35-38).

One of ordinary skill in the art would have a reasonable expectation of success as methods of construction of a bacterial expression vector is different from that for the construction of mammalian expression vectors etc. all of which are constructed in accordance with techniques well known in the art. (See Crawford, col. 6, lines 42-53). Additionally, Robbins et al. in their recent review on viral vectors, have described the construction of retroviral vectors and their efficacy in gene transfer. (See Robbins et al. page 35, col. 2 and 36, fig 1).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to insert the IKB-kinase alpha gene, which acts as an inhibitor of NF-kappa B, into a retroviral vector.

8. Claims 20 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crawford et al. (U.S. Pat. No: 6,107, 057), in view of Robbins et al.

Claim 26 is directed to a retroviral vector comprising a nucleic acid molecule encoding an inhibitor of IL-1 beta activity wherein the inhibitor is an insulin like growth

factor-1 protein (IGF-1). Claim 20 is directed to a retroviral vector comprising a nucleic acid molecule encoding any inhibitor of IL-1 beta activity.

Crawford taught a heterologous nucleotide sequence such as IGF-1 gene (insulin like growth factor) cloned into an autonomously replicating vector. (See col. 8, lines 29-34).

Crawford does not expressly disclose that the IGF-1 gene is inserted into a retroviral vector.

However, recombinant DNA technology has revolutionized the way genes can be inserted into different vectors and expressed by means of specified promoters.

One of ordinary skill in the art would have been motivated to do this as Crawford stated that methods for introducing heterologous polynucleotides into mammalian cells are known in the art and include viral infection. (See col. 6, lines 35-38).

One of ordinary skill in the art would have a reasonable expectation of success as methods of construction of a bacterial expression vector is different from that for the construction of mammalian expression vectors etc. all of which are constructed in accordance with techniques well known in the art. (See Crawford, col. 6, lines 42-53). Additionally, Robbins et al. in their recent review on viral vectors, have described the construction of retroviral vectors and their efficacy in gene transfer. (See Robbins et al. page 35, col. 2 and 36, fig 1).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to insert the IGF-1 gene into a retroviral vector.

Conclusion

9. Claims 1-12 and 20-30 are rejected.

10. Claims 1-12 as filed are free of the prior art of record. At the time of filing, the prior art did not teach or suggest a method for reducing beta-cell dysfunction in an individual with a pancreatic disorder by introducing a nucleic acid molecule encoding an inhibitor or IL-1 beta into a beta cell and transplanting the beta cell into an individual so as to reduce beta-cell dysfunction.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eleanor Sorbello, whose telephone number is 703-308-6043. The examiner can normally be reached on Monday-Friday from 6.30 A.M. to 3.00 P.M. (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Eleanor Sorbello

DEBORAH J.R. CLARK
PRIMARY EXAMINER